

Ly6d marks the earliest stage of B-cell specification and identifies the branchpoint between B-cell and T-cell development.

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Public Summary:

All mature blood cells are produced from a single cell type, the hematopoietic stem cell (HSC). HSCs differentiate to mature blood cells through a series of intermediate progenitor stages. Within these intermediate states, a network of gene expression changes occurs and establishes the both identity of the mature fate (specification) and prevents the development of alternate lineages (commitment). As such, these developmental intermediates can be viewed as nodes, or branchpoints in which major fate decisions are made. Understanding how these fate decisions are made requires the ability to precisely identify and isolate the intermediate branchpoints. One branchpoint is the decision to generate either B cells or T cells. The Common Lymphocyte Progenitor (CLP) is the cell type thought to reside at this developmental branchpoint. However, many groups question whether CLP even exist, and propose that another intermediate, the Lymphoid-primed Multipotent Progenitor (LMPP) is the cell type that gives rise to all lymphocytes and myeloid cells. We hypothesized that much of the controversy surrounding the existence of CLPs was based on a contamination of this population of cells with another cell type which is already committed to the B cell lineage. We therefore sought a method to separate true CLP from the hypothesized contaminating B cell progenitor. MiDReG (Mining Developmentally Regulated Genes) is an algorithm designed to identify developmentally regulated genes using existing publically-available microarray gene expression databases. We used MiDReG to identify genes upregulated in B cell development that we could potentially use to purify true CLP. One gene predicted by MiDReG to be upregulated in B cell development is Ly6d. We examined Ly6d expression in CLP and discovered that it separated CLP into two distinct populations. We nicknamed Ly6d- CLP "ALP" and Ly6d+ CLP "BLP" based on our predicted lineage relationship (i.e. that ALP precede BLP). We found that BLP behaved essentially as a B cell progenitor, and produced primarily B cells when transplanted intravenously into recipient mice. Alternatively, ALP produced all lymphoid lineages (B cell, T cell, Natural Killer cell, and dendritic cell), but no myeloid lineages when intravenously transplanted. When BLP were transplanted directly into the thymus, an environment that strongly drives cells toward the T cell lineage, B cells were primarily produced, suggesting that BLP were committed to the B cell lineage. ALP produced almost exclusively T cells when intrathymically transplanted, suggesting that they are uncommitted. Our results indicate that CLP can be subdivided into two populations, in which Ly6d+ "BLP" are B cell progenitors and Ly6d- "ALP" behave as true CLP. By examining gene expression in ALP and BLP, we found that most B cell specific transcription factors are upregulated between ALP and BLP, suggesting that this step is when B cell specification occurs. Furthermore, ALP appears to be the population that resides at the developmental branchpoint between B cell and T cell development. Thus, as the title indicates, Ly6d marks the earliest stage of B cell specification (BLP), and identifies the branchpoint between B-cell and T-cell development (ALP).

Scientific Abstract:

Common lymphoid progenitors (CLPs) clonally produce both B- and T-cell lineages, but have little myeloid potential in vivo. However, some studies claim that the upstream lymphoid-primed multipotent progenitor (LMPP) is the thymic seeding population, and suggest that CLPs are primarily B-cell-restricted. To identify surface proteins that distinguish functional CLPs from B-cell progenitors, we used a new computational method of Mining Developmentally Regulated Genes (MiDReG). We identified Ly6d, which divides CLPs into two distinct populations: one that retains full in vivo lymphoid potential and produces more thymocytes at early timepoints than LMPP, and another that behaves essentially as a B-cell progenitor.